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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,131	10/11/2005	Maria-Jesus Blanco-Pillado	X-14441	7160

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EXAMINER	
CHANG, CELIA C	
ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
02/14/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@lilly.com

Office Action Summary	Application No.	Applicant(s)	
	10/552,131	BLANCO-PILLADO ET AL.	
	Examiner	Art Unit	
	Celia Chang	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,9,14,15 and 29-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 9, 14-15, 29-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Amendment and response filed by applicants dated Nov. 28, 2007 have been entered and considered carefully.

Claims 2-8, 10-13, and 16-28 have been cancelled.

Claims 1, 9, 14-15, and newly added claims 29-32 are pending.

2. Claims 1, 9, 14-15, and 29-32 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Please note that mix and matching Markush elements without explicit antecedent basis for the subgeneric scope is considered new matter. It is noted that, on page 14 preference number 42, the scope of R1, R2, R3, R4a, R4b, R4c, R5 have been disclosed while R6 is not limited to hydrogen. On page 12, the specific R1 preference for claims 29-32 was disclosed without any specific subgeneric combination with the other moieties. Further, there if no data or binding efficacy which provided guidance in the specification that the now amended new scope has particular activity as to support the instant scope having the amended method of treating/preventing migraine.

This is a NEW MATTER rejection. Removal of all new matter is required. In re Russemussen 210 USPQ 325.

3. After removal of new matter and the claims are restored to the previous version, the rejection of record:

Claims 1-4 under 35 U.S.C. 102(b) as being clearly anticipated by Pruecher et. al. CA 122L265361; Gaster et al. CA 130:13850; Eriksson et al. or CA 137:247696;

Claims 1-5 and 9 under 35 U.S.C. 102 (a), (b) or (e) as being anticipated by Chen CA 137:216945 or the issued US 7,105,682 (col. Col. 146, #74); or Askew et al. CA 140:16647 or the issued US 6,878,714 (col. 287 #533);

Claims 1-7, 9, 14-15 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement; and

Claims 14-15 under 35 USC 112 first paragraph for the scope of preventing;

are maintained for reason of record.

It has been explained in section 2 that mixing and matching Markush elements without explicit antecedent basis for the sub-generic scope is considered new matter for the amended compound claims (See CA 141:395422 and exemplified structural delineation of the instant application, a wide variety of compounds without any particularity was disclosed). Further, no description or factual evidence were found in the specification as to offer guidance to the particular scope being of choice for treating/preventing migraine. Applicants argued that on page 166 line 11 through page 167 line 25, in vivo method was disclosed. However, no efficacy data supporting the instantly amended scope was found for the disclosed testing process nor any structure-activity relationship provides such support (see CAPLUS AN 2004:226622).

4. Claims 29-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916), where the Supreme Court looked to whether the experimentation needed to practice an invention was undue or unreasonable. *Id.* An invention must be described so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). As stated in the MPEP 2164.01(a) "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". The analysis must consider all the evidence related to each of these factors, and any conclusion of non-enablement must be based on the evidence as a whole. *Id.* at 740, *Id.* at 1407. The factors to be considered herein are those set forth as the In re Wands, 8 USPQ 2nd 1400 (1988) decision.

The analysis is applied to the instant case.

Nature of invention

The claims are drawn to compounds having structure of claim 29 and their use in treating/preventing migraine.

The state of the art and predictability

Compounds for CNS activity is a highly unpredictable field of endeavor. Ordinarily, compounds which can be used in treating CNS disorder, such as migraine, is well recognized in the art that such compound must have in vivo activity, i.e crossing the blood brain barrier as to reach the target organ (see LY344864 having in vivo activity, Phebus et al. CA 128:18603, recited in the previous office action). Recent development in the field of 5HT1F receptor agonist activity indicated there is a very rigid structure-activity relationship between the binding compound and the receptor (see Blanco CAPLUS).

The amount of guidance and working examples

The specification provided no *in vivo* activity that the newly added sub-generic scope of compounds have any in vivo crossing of the blood and brain barrier or any correlation between the in vitro data to the in vivo data (see Wainscott et al. or Cohen et al. CA 131:266942 recited in previous office action), nor any SAR analysis providing sufficient guidelines as to how to use the compounds or how to operate the method of treating/preventing migraine. Please note that the Blanco et al. reference provided strong evidence by SAR of the rigidity in receptor binding. Absent of any SAR information, no support for any non-disclosed mixing and matching of the Markush elements having analogous activity/efficacy in treating migraine can be found.

6. Claims 31-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as well as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention; or the subject matter was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The scope of claims 31-32 include "prevention" of migraine. Medically preventing any pathological condition must provide description and enabling teaching in identifying such population which preventions is applicable; dosage and toxicity for effectively ward off symptom or disease; and absolutely no incidence of symptom or disease when the preventive measure is taken. No description in the specification as to who are the candidates that

constitutes de novo prevention, what dosage without toxicity for how long so that zero incidence was obtained. Absent of such critical description and enablement, the specification failed to provide descriptive and enabling support for the claimed scope of "prevention" migraine.

Please note that a maintenance dose after diagnosis of a pathology to prevent future symptom is considered maintenance treatment and encompassed by the scope of *treatment.*

Applicants provided statements from the Migraine association website which support the rejection since preventive treatment is for those "patients who have frequent headaches" which is considered a *maintenance* treatment to prevent symptoms, thus, is considered encompassed by the scope of treatment of migraine. There is no good reason to give any *human* any preventive dose i.e. *de novo prevention*, if the person does not have migraine.

7. Claims 9 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are self conflicting because they are "pharmaceutical" composition without a quantitative limitation. A pharmaceutical composition must contain neither an ineffective nor a toxic amount of the active ingredients. It is recommended that a quantitative limitation such as "5HT1F receptor agonistic effective amount", "an anti-migraine effective amount" etc. be incorporated.

8. Applicants' amendments and new claims necessitated the new grounds of rejections.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celia Chang, Ph. D. whose telephone number is 571-272-0679. The examiner can normally be reached on Monday through Thursday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres, Ph. D., can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

OACS/Chang
Feb. 11, 2008

/Celia Chang/
Primary Examiner
Art Unit 1625